Published Abstract

Investigation of the Prevalence of Positive Results from the Gadd45a-gfp “greenscreen Hc” Genotoxicity Assay Amongst Nsaids, Apoptogens and Hdac Inhibitors.

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Introduction: Increased GADD45a expression provides sensitive and specific identification of genotoxic carcinogens. This report summarises an investigation designed to identify and test compounds with the potential to produce misleading positive GADD45a results. Methods: Compounds were identified that either induce GADD45a in assays other than GreenScreen HC, or affect pathways in which GADD45a is active but have not previously been tested. Data were collected by experiment/literature review. Results: NSAIDs are not genotoxic carcinogens, but indomethacin and sulindac sulphide (active metabolite of sulindac) induce GADD45a mRNA/protein synthesis in human colon cancer cell lines. Eighteen of nineteen (95%) NSAIDs (including metabolites) produced negative GADD45a results–specificity similar to published validation studies. GADD45a is involved in the DNA damage response, and regulation of apoptosis, however apoptosis can also be triggered by nongenotoxic agents. Compounds hypothesized to stimulate apoptosis via GADD45a in the absence of genotoxic stress were tested, including p53 activators, NF-κB/Bcl-2 inhibitors, etc. Most were research compounds, with no associated genotoxicity/ carcinogenicity data. Twelve were negative in the GADD45a-GFP assay. Four produced positive results and were also positive in concurrent comet and/or MNT: the GADD45a-GFP assay is not specifically liable in this class. HDAC inhibitors affect chromatin structure, plausibly interfering with DNA repair–an indirect mechanism of genotoxicity. GADD45a produced positive results for 4 HDACi: trichostatin A (MNT/CA positive), apicidin (CA positive in vivo), sodium butyrate (MNT positive in CHO and L929), and APHA compound 8 (no published data found). Conclusion: The study did not reveal class specific liabilities in the GADD45a-GFP assay.